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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : U.S. Serial Number 09/308,223
Applicant : Georg KALLMEYER et al
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TC/A.U. : 1642
Examiner : Brandon J. Fetterolf

Docket No. : 2924-139
Customer No. : 6449
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

April 28, 2006

Dear Sir:

Applicants hereby request review of the final rejection in the above identified application. No amendments are being filed with this request. This request is being filed along with a notice of appeal. The review is requested for the reasons stated on the attached sheets.

In the event that any fees may be due with respect to this paper, such fees may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By

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REASONS FOR REQUESTING A PRE-APPEAL BRIEF REVIEW

In the only remaining rejection, claims 13, 15-18 and 22-36 were rejected under 35 USC §103(a) as unpatentable over Andya in view of Michaelis. Claims 13, 15-18 and 22-36 are directed to a lyophilizate which contains a monoclonal or polyclonal antibody, an amino sugar, at least one amino acid, and a surfactant, where the lyophilizate does not contain polyethylene glycols or additional proteins; a composition containing the lyophilizate and a method for preparing the lyophilizate. The office actions contend that one skilled in the art would be motivated to combine Andya and Michaelis to arrive at the present invention because both of these references teach the preparation of stable pharmaceutical compositions. Applicants respectfully point out that Michaelis discloses the addition of an amino sugar to stabilize a protein (G-CSF) not antibodies while Andya is directed to antibody preparations which do not contain amino sugars.

The Office Action states that it would have been obvious to modify the lyophilizate of Andya to include an amino sugar as taught by Michaelis. Michaelis discloses the addition of an amino sugar to stabilize a protein not antibodies. Applicants respectfully point out that among proteins different stabilizers are required, not all stabilizers are suitable for all proteins. Osterberg (WO 94/07510) states on page 4, lines 25-32 that:

"Proteins are different with regard to physico-chemical properties. When preparing a pharmaceutical preparation which should be physico-chemical acceptable, and stable for a long time, consideration cannot only be taken to the physiological properties of the protein but also other aspects must be considered such as the industrial manufacture, easy handling for the patient and safety for the patient. **The results of these aspects are not predictable when testing different**

formulations and there often is a unique solution for each protein," (emphasis added).

Osterberg points out that different proteins are different in their physico-chemical properties and thus for each protein or class of proteins an individual solution has to be developed and thus it cannot be predicted that the same formulation will be useful for a different class of proteins.

Manning (Pharmaceutical Research, Vol. 6, No. 11, 1989, p. 903-918) is a general article related to the stability of proteinaceous pharmaceuticals. On page 913, left column, first sentence of the last paragraph, it is stated that "protein stability encompasses many complicated and interrelated chemical and physical processes". From this it can be concluded that for every protein or class of proteins an individual solution has to be found due to different physical and chemical constraints. Thus, one skilled in the art would not extrapolate the disclosure in Michaelis to any and all proteins and certainly not to any and all pharmaceutical compositions as suggested in the office actions.

Osterberg's and Manning's conclusions are supported by the fact that different substances are indicated as good stabilizers in some references and as not useful as a stabilizer in other references. For example, Kunihiro (EP 0 689 843) page 4, line 4 - 7, indicates that the combination of soluble thrombomodulin together with albumin, purified gelatin, glycine, glucose or mannitol **failed** to exhibit sufficient long term stability. Thus, this document contradicts the contention in the office actions that Michaelis' teaching can be applied to any and all pharmaceutical

preparations. Kunihiro teaches away from the current invention in that the combination of an amino acid with a sugar had no beneficial effect on stability.

Hanson (chapter 7 in Stability of Protein Pharmaceuticals, 1992) indicates on page 217, second paragraph, line 6 to 7 that "Ornithine, aspartic acid, glutamic acid, alanine and glycine did not stabilize" intravenous immunoglobulin preparations. Thus, Hanson also contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations and teaches away from the current invention which shows that the use of the amino acids listed in Hanson improve the stability of the lyophilized antibody formulation.

Metzner (EP 0 733 702) which is equivalent to US Patent No. 6,204,036 indicates that histidine and glutamic acid alone, even without further additives, show sufficient stabilization (page 3, line 9, of the German text, column 5, lines 56-58 of the US text). In contrast to Metzner, Michaelis (WO 94/14465) states on page 10, lines 4 to 7 of the German WO 94/14465 that the addition of glutamic acid has no significant impact on the storage stability. Both Metzner and Michaelis also indicate that the surfactant had no impact on storage stability (Metzner page 3, lines 42-43 or col. 6, lines 48-50 in the U.S. Patent, Michaelis page 9, last paragraph of WO 94/14465) but the present inventors have found that the surfactant does affect stability in the present invention. Thus, formulations for stabilizing different pharmaceutical preparations clearly cannot be generalized.

Nema (J. Parent Sci. Technol., 47, p. 76-83, 1993) states on page 81, left column, last sentence of the first paragraph: "A surprising result was obtained with trehalose, a disaccharide which is considered by many workers to be one of the best

cryoprotectants, but proved to be ineffective in this study at a concentration of 5%w/v". This statement also supports the conclusion of the non-transferability of formulations to different classes of proteins.

Three things can be concluded from the above discussed references:

1) There is no suggestion that a combination of different compounds discussed in different references will result in a formulation with further improved stability. Furthermore there is no hint in these documents as to the particular combination of compounds as described in the current invention.

2) As can be seen from these references, it is not possible to transfer the composition of a formulation useful with one class of proteins or with one protein to other proteins. It is not probable or even predictable that such a transfer might be successful with the antibody preparation of the present invention.

3) There are no cited documents that suggest or disclose that a formulation for stabilizing a non-antibody protein can be used for the stabilization of a lyophilized antibody preparation.

Applicants also point out that Andya teaches at column 29, lines 49-50, that "reducing sugars are not suitable as lyoprotectants for the antibody". In contrast to this, the present inventors have found that amino sugars derived from reducing sugars such as glucose or galactose are suitable for use in the present invention.

Applicants contend that one skilled in the art would not expect Michaelis' formulation to be useful for any and all pharmaceutical preparations as different proteins require different stabilization agents and there is no reason to believe that Michaelis' formulation would stabilize antibody preparations such as Andya's

antibody formulation. In view of the above discussion, applicants request that this rejection be withdrawn.